

# Activin Directs Development by Encoding Cell Location

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Cells must sense their position and differentiate into the appropriate cell type in developing embryos. The embryo must establish a coordinate system and individual cells must have the ability to sense, and correctly interpret, the positional information. Knowing their location, cells may then enhance, or inhibit, the proper genes for their designated cell type. One way to encode locations is to emit a signal molecule from a point source able to passively diffuse throughout the embryo. Target cells will then be able to sense their distance from the source by measuring the signal molecule's concentration. Activin is such a signal molecule. Gurdon et al. (1994) and Dyson and Gurdon (1998) have demonstrated expression of particular genes are related to the concentration of activin the cells receive. A gradient of activin is capable of directing cell differentiation.

*Activin diffuses passively through tissue.*

Gurdon et al. (1994) used an activin mRNA injection assay to establish the passive diffusion gradient in embryos. They showed activin-induced gene expression occurs in target tissue even when it is separated from the activin source by non-competent cells. This eliminated the possibility of induction occurring by active relay amplification of the signal. Additionally, beads containing activin produced the same gene expression pattern as the injecting experiments, further supporting the passive diffusion model of activin.

*Genes are activated by particular concentrations of activin.*

Each gene activated by the activin gradient responds to its own quantitative amount of activin. Gurdon et al. (1994) compared expression of *Xbrachyury* (*Xbra*) and *Xgooseoid* (*Xgsc*) in animal cap cells injected with various amounts of activin mRNA. Neither gene was expressed without activin mRNA, but peak expression of *Xbra* occurred at about half the amount of activin mRNA required to maximally express *Xgsc*. Furthermore, *Xbra* expression was very low when *Xgsc* expression peaked. This shows expression of different genes is controlled by particular concentrations of activin. Since activin concentration is spatially related, then expression of activin-activated genes is also relative to the position of the morphogen's source.

*Gene activation is determined by a single type of receptor.*

An alternate way for cells to sense their position is to respond to an inducer with receptors having different ligand affinities. These different receptors might then send cells on separate developmental pathways. Dyson and Gurdon (1998) tested whether cells respond to the activin inducer with only one, or with several, receptors. They overexpressed one of two different activin receptors (type I or type II) in blastula cells, injected activin mRNA, then assayed for bound activin. Increasing the concentration of type II receptors also increases the amount of bound activin, but type I receptor overexpression did not change the amount of bound activin. This experiment shows cells sense the activin gradient through one receptor type exhibiting a single affinity for activin. Additionally, activin has high affinity for its receptor and stays bound for a long duration allowing cells to respond to the highest activin concentration.

*Cells detect absolute receptor occupancy.*

Detecting the surrounding concentration of activin through bound receptors might be done in two ways. Cells may sense the ratio of bound to unbound receptors, or they could simply count the number of ligand-bound receptors. Dyson and Gurdon (1998) tested these alternatives by comparing normal and receptor-injected cells. The increase in unbound receptors in injected cells would change the cell's response to activin in the ratio model; no change would occur if cells sensed only the absolute number of bound receptors. They saw no change in *Xbra* or *Xgsc* expression with increased receptor expression. Cells, therefore, sense activin concentration by sensing the absolute number of bound receptors.

*Morphogenic gradients are capable of directing development.*

These experiments show how a molecule emanating from a single source can indicate the developmental direction cells must take. Activin passively diffuses through tissue, where target cells sense its concentration by counting their absolute number of bound receptors. Signals from the receptors then direct gene expression. Some genes are expressed when activin concentration is high, others when activin is scarce. In this way, cells know their position in the embryo and can differentiate into the appropriate cell type.

*How does the activin signal initiate gene expression?*

Dyson and Gurdon (1998) showed cells respond to the highest concentration of activin in their environment. The specific mechanism cells use to sense the number of occupied receptors, however, is still unknown. Though they did not find any direct binding of activin to type I receptors, the authors suggest type I receptors may somehow help type II receptors sense activin concentration. This can be tested by overexpressing various mutant type I receptors and looking for changes in expression of *Xbra* and *Xgsc*. Type I receptor mutations causing a lack of activin response would indicate domains involved in activin sensing. This experiment could help elucidate the mechanism cells use to regulate gene expression based on activin concentration.

## Literature Cited

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